EXHIBIT D

View of NCT01494805 on 2011_12_16

ClinicalTrials Identifier: NCT01494805
Updated: 2011_12_16

Descriptive Information

Brief title Safety and Efficacy Study of rAAV.sFlt-1 in Patients With Exudative Age-Related Macular Degeneration

Official title A Phase I/II Controlled Dose-escalating Trial to Establish the Baseline Safety and Efficacy of a Single Subretinal Injection of rAAV.sFlt-1 Into Eyes of Patients With Exudative Age-related Macular Degeneration (AMD)

Brief summary

The study will involve 24 patients aged 65 or above who have exudative age-related macular degeneration (wet AMD). Patients will be randomized to receive one of two doses of rAAV.sFlt-1 (16 patients) or assigned to the control group (8 patients). Patients in all three groups are eligible for rescue therapy with ranibizumab.

Detailed description

A new treatment for exudative age-related macular degeneration (wet AMD) is being investigated. The purpose of this Phase I/II clinical research study is to examine the baseline safety and efficacy of an experimental study drug to treat a complication of the disease which leads to vision loss. The name of the study drug is rAAV.sFlt-1.

This experimental study uses a non-pathogenic virus to express a therapeutic protein within the eye. The therapeutic is a naturally-occurring protein intended to diminish the growth of abnormal blood vessels under the retina. The duration of effect is thought to be long-term (years) following a single administration. The therapeutic is delivered to a small area underneath the retina (subretinal) in a short surgical procedure.

The clinical research study will look at the baseline safety and efficacy of a single injection of rAAV.sFlt-1 injected directly into the eye. There are 3 steps to this study. In the first step, patients will receive either low dose rAAV.sFlt-1 or control treatment. In the second step, patients will receive either the high dose rAAV.sFlt-1 or control treatment. In the third step patients will receive either the low dose rAAV.sFlt-1, the high dose rAAV.sFlt-1, or control treatment. Patients in all groups will be eligible for rescue therapy with ranibizumab throughout the study.

Twenty-four (24) patients will participate at 1 center in Australia. The primary

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endpoint of the study is at one month, with extended follow up for 3 years.

Phase	Phase 1
Phase	Phase 2
Study type	Interventional
Study design	Treatment
Study design	Randomized
Study design	Single Blind (Outcomes Assessor)
Study design	Parallel Assignment
Study design	Safety/Efficacy Study
Primary outcome	Measure: No sign of unresolved ophthalmic complications, toxicity or systemic complications as measured by laboratory tests from 1 month post injection Time Frame: Primary endpoint at 1 month Safety Issue? Yes Description: 1) Ocular examination: - Ocular inflammation - Intraocular pressure - Visual acuity - Retinal bleeding 2) Abnormal laboratory data
Secondary outcome	Measure: Maintenance or improvement of vision without the necessity of ranibizumab re-injections Time Frame: Up to 3 years Safety Issue? No Description: 1) Best-corrected visual acuity 2) CNV lesion 3) Foveal thickness
Enrollment	24 (Anticipated)
Condition	Macular Degeneration
Condition	Age-related Maculopathies
Condition	Age-related Maculopathy
Condition	Maculopathies,Age-related
Condition	Maculopathy,Age-related
Condition	Retinal Degeneration
Condition	Retinal Neovascularization
Condition	Eye Diseases
Arm/Group	Arm Label: Low Dose rAAV.sFlt-1 Experimental
Arm/Group	Arm Label: High Dose rAAV.sFlt-1 Experimental

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Arm/Group	Arm Label: Control - ranibizumab only	Active Comparator
Intervention	Biological/Vaccine: rAAV.sFlt-1 rAAV.sFlt-1 1 x 10^10 vector genomes (vg) rAAV.sFlt-1, delivered by subretinal injection	Arm Label: Low Dose
Intervention	Biological/Vaccine: rAAV.sFlt-1 rAAV.sFlt-1 1 x 10^11 vector genomes (vg) rAAV.sFlt-1, delivered by subretinal injection	Arm Label: High Dose
Intervention	Other: Control (ranibizumab alone) Patients will not receive rAAV.sFlt-1, but will be eligible for retreatment with ranibizumab (Lucentis).	Arm Label: Control - ranibizumab only

Recruitment Information

Status	Recruiting
Start date	2011-12
Last follow-up date	2014-12 (Anticipated)
Primary completion date	2012-12 (Anticipated)

Criteria

Inclusion Criteria:
• Age greater than or equal to 65 years;
• Subfoveal CNV secondary to AMD and with best corrected visual acuity of 3/60 - 6/24 with 6/60 or better in the other eye;
• Fluorescein angiogram of the study eye must show evidence of a leaking subfoveal choroidal neovascular lesion;
• Must be a candidate for anti-VEGF intravitreal injections;
• The entire dimension of the lesion must not exceed 12 Macular Photocoagulation Study disc areas;
• No previous retinal treatment of photodynamic therapy or laser;
• Able to provide informed consent;
• Participant has clinically acceptable laboratory and ECG at the time of enrolment; and
• Able to comply with protocol requirements, including follow-up visits.

Exclusion Criteria:
• Liver enzymes > 2 X upper limit of normal;
• Clinical evidence of active infection of any type, including adenovirus, hepatitis A, B, or C, or HIV virus;
• Any prior treatment for AMD in the study / control eye, excluding anti-VEGF injections;
• A tear in the retinal pigmented epithelium;

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• Extensive submacular scar tissue;
• Significant retinal disease other than subfoveal CNV AMD, such as diabetic retinopathy or retinal vascular occlusion;
• Significant non-retinal disease such as ocular atrophy or cataracts;
• Known allergy to fluorescein;
• Current use of prednisolone, other anti-inflammatory steroids or immune suppression drugs. Non-steroidal drugs such as aspirin are allowed;
• Any other significant disease or disorder which, in the opinion of the Investigator, may either put the participants at risk because of participation in the study, or may influence the result of the study, or the participant's ability to participate in the study;
• Participants who have participated in another research study involving an investigational product in the past 12 weeks; and
• Penicillin sensitivity.

Gender	Both
Minimum age	65 Years
Healthy volunteers	No

Administrative Data

Organization name	Lions Eye Institute, Perth, Western Australia
Organization study ID	2008-135
Sponsor	Lions Eye Institute, Perth, Western Australia
Collaborator	Avalanche Biotechnologies, Inc.
Health Authority	Australia: Department of Health and Ageing Therapeutic Goods Administration

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← History of this study ↑ Current version of this study

- [x] Hide unchanged portions (except top/bottom lines)
- [x] Hide non-essential portions (contact info, locations, etc.)

Changes to NCT01494805 on 2012_09_11

Type of info changed: Protocol, Recruitment, Administrative, Misc.

	Before (Updated 2011_12_16)	After (Updated 2012_09_11)
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	<nct_id>	<nct_id>
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3	</nct_id>	</nct_id>
	<textblock>	<textblock>
4	The study will involve 24 patients aged 65 or above who have exudative age-related macular degeneration (wet AMD). Patients will be randomized to receive one of two doses of rAAV.sFlt-1 ~~(16 patients)~~ or assigned to the control ~~group (8 patients). Patients in all three groups are eligible for rescue therapy with ranibizumab.~~	The study will involve 48 patients aged 55 or above who have exudative age-related macular degeneration (wet AMD). Patients will be randomized to receive one of two doses of rAAV.sFlt-1 or assigned to the control group.
5	</textblock>	</textblock>
6	This experimental study uses a non-pathogenic virus to express a therapeutic protein within the eye. The therapeutic ~~is a naturally-occurring protein intended to diminish~~ the growth of abnormal blood vessels under the retina. The duration of effect is thought to be long-term (years) following a single administration. ~~The therapeutic is delivered to a small area underneath the retina (subretinal) in a short surgical procedure.~~	This experimental study uses a non-pathogenic virus to express a therapeutic protein within the eye. The therapeutic diminishes the growth of abnormal blood vessels under the retina. The duration of effect is thought to be long-term (years) following a single administration.
7		
8	The clinical research study will look at the baseline safety and efficacy of a single injection of rAAV.sFlt-1 injected directly into the eye. ~~There are 3 steps to this study. In the first step, patients will receive either low dose rAAV.sFlt-1 or control treatment. In the second step, patients will receive either the high dose rAAV.sFlt-1 or control treatment. In the third step patients will receive either the low dose~~	The clinical research study will look at the baseline safety and efficacy of a single injection of rAAV.sFlt-1 injected directly into the eye.

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	~~rAAV.sFlt-1, the high dose rAAV.sFlt-1, or control treatment. Patients in all groups will be eligible for rescue therapy with ranibizumab throughout the study.~~	
9		
10	**Twenty-four (24)** patients will participate ~~at 1 center~~ in Australia. The primary endpoint of the study is at one month, with extended follow up for 3 years.	**Forty-eight (48)** patients will participate in Australia. The primary endpoint of the study is at one month, with extended follow up for 3 years.
11	</textblock> <date>	</textblock> <date>
12	**2011-12**	**2012-09**
13	</date> <date>	</date> <date>
14	**2012-12**	**2013-06**
15	</date> >	</date> >
16	**24**	**48**
17	</enrollment> Inclusion Criteria:	</enrollment> Inclusion Criteria:
18	• Age greater than or equal to **65** years; • Subfoveal CNV secondary to AMD and with best corrected visual acuity of 3/60 - **6/24** with 6/60 or better in the other eye; • Fluorescein angiogram of the study eye must show evidence of a leaking subfoveal choroidal neovascular ~~lesion;~~	• Age greater than or equal to **55** years; • Subfoveal CNV secondary to AMD and with best corrected visual acuity of 3/60 - **6/9** with 6/60 or better in the other eye; • Fluorescein angiogram of the study eye must show evidence of a leaking subfoveal choroidal neovascular **lesion, or CNV currently under active management with anti-VEGF therapy;**
19	• Must be a candidate for anti-VEGF intravitreal injections;	• Must be a candidate for anti-VEGF intravitreal injections;
20	• The entire dimension of the lesion must not exceed 12 Macular Photocoagulation Study disc areas;	
21	• No previous retinal treatment of photodynamic therapy or laser; • Able to provide informed consent;	• No previous retinal treatment of photodynamic therapy or laser; • Able to provide informed consent;
22	• Participant has clinically acceptable laboratory and ECG at the time of enrolment; and	
23	• Able to comply with protocol requirements, including follow-up visits. • Liver enzymes > 2 X upper limit of normal;	• Able to comply with protocol requirements, including follow-up visits. • Liver enzymes > 2 X upper limit of normal;
24	• Clinical evidence of active	

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	infection of any type, including adenovirus, hepatitis A, B, or C, or HIV virus;	
25	• Any prior treatment for AMD in the study / control eye, excluding anti-VEGF injections;	• Any prior treatment for AMD in the study / control eye, excluding anti-VEGF injections;
26	• A tear in the retinal pigmented epithelium; • Extensive submacular scar tissue; • Significant retinal disease other than subfoveal CNV AMD, such as diabetic retinopathy or retinal vascular occlusion; • Significant non-retinal disease such as ocular atrophy or cataracts; • Known allergy to fluorescein; • Current use of prednisolone, other anti-inflammatory steroids or immune suppression drugs. Non-steroidal drugs such as aspirin are allowed; • Any other significant disease or disorder which, in the opinion of the Investigator, may either put the participants at risk because of participation in the study, or may influence the result of the study, or the participant's ability to participate in the study; • Participants who have participated in another research study involving an investigational product in the past 12 weeks; and • Penicillin sensitivity.	
27		• Extensive sub-foveal scarring, extensive geographic atrophy, or thick subretinal blood in the study eye as determined by the investigator; • Significant retinal disease other than sub-foveal CNV AMD;
28	</textblock> <minimum_age>	</textblock> <minimum_age>
29	**65** Years	**55** Years
30	</minimum_age> <last_release_date>	</minimum_age> <last_release_date>
31	**2011-12-15**	**2012-09-11**
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Changes to NCT01494805 on 2013_12_19

Type of info changed: Misc.

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4		<is_section_801> No </is_section_801>
5	<brief_title>	<brief_title>
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6	2014-12	2016-12
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8	2013-06	2014-06
9	</date>	</date>
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Key

	Before	After
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2	Deleted.	
3	Changed from this...	...to this.
4		Added.
...	...	...

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- [x] Hide unchanged portions (except top/bottom lines)
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Changes to NCT01494805 on 2014_02_25

Type of info changed: Protocol, Misc.

	Before (Updated 2013_12_19)	After (Updated 2014_02_25)
1	<clinical_study>	<clinical_study>
2	~~Forty-eight~~ (48) patients will participate in Australia. The primary endpoint of the study is at one month, with extended follow up for 3 years.	A minimum of thirty-nine (39) and up to forty-eight (48) subjects will participate in Australia. The primary endpoint of the study is at one month, with extended follow up for 3 years.
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4	2016-12	2017-04
5	</date> <date>	</date> <date>
6	2014-06	2015-04
7	</date> <keyword>	</date> <keyword>
8		AAV </keyword> <keyword>
9	AMD <last_release_date>	AMD <last_release_date>
10	2013-12-18	2014-02-24
11	</last_release_date> </clinical_study>	</last_release_date> </clinical_study>

Key

	Before	After
1	Unchanged.	Unchanged.
2	Deleted.	
3	Changed from this...	...to this.
4		Added.

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← History of this study ↑ Current version of this study

- [x] Hide unchanged portions (except top/bottom lines)
- [x] Hide non-essential portions (contact info, locations, etc.)

Changes to NCT01494805 on 2014_03_18

Type of info changed: Protocol, Misc.

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	<textblock>	<textblock>
2	The study will involve ~~48 patients~~ aged 55 or above who have exudative age-related macular degeneration (wet AMD). Patients will be randomized to receive one of two doses of rAAV.sFlt-1 or assigned to the control group.	The study will involve **approximately 40 subjects** aged 55 or above who have exudative age-related macular degeneration (wet AMD). Patients will be randomized to receive one of two doses of rAAV.sFlt-1 or assigned to the control group.
3	</textblock>	</textblock>
4	~~A minimum of thirty-nine (39) and up to forty-eight (48)~~ subjects will participate in Australia. The primary endpoint of the study is at one month, with extended follow up for 3 years.	**Approximately forty (40)** subjects will participate in Australia. The primary endpoint of the study is at one month, with extended follow up for 3 years.
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	>	>
10	**48**	**40**
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Key

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← History of this study ↑ Current version of this study

- [x] Hide unchanged portions (except top/bottom lines)
- [x] Hide non-essential portions (contact info, locations, etc.)

Changes to NCT01494805 on 2014_04_09

Type of info changed: Recruitment status, Misc.

	Before (Updated 2014_03_18)	After (Updated 2014_04_09)
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3	</status> <last_release_date>	</status> <last_release_date>
4	2014-03-17	2014-04-09
5	</last_release_date> </clinical_study>	</last_release_date> </clinical_study>

Key

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View of NCT01494805 on 2014_04_09

ClinicalTrials Identifier: NCT01494805
Updated: 2014_04_09

Descriptive Information

Brief title Safety and Efficacy Study of rAAV.sFlt-1 in Patients With Exudative Age-Related Macular Degeneration

Official title A Phase I/II Controlled Dose-escalating Trial to Establish the Baseline Safety and Efficacy of a Single Subretinal Injection of rAAV.sFlt-1 Into Eyes of Patients With Exudative Age-related Macular Degeneration (AMD)

Brief summary

The study will involve approximately 40 subjects aged 55 or above who have exudative age-related macular degeneration (wet AMD). Patients will be randomized to receive one of two doses of rAAV.sFlt-1 or assigned to the control group.

Detailed description

A new treatment for exudative age-related macular degeneration (wet AMD) is being investigated. The purpose of this Phase I/II clinical research study is to examine the baseline safety and efficacy of an experimental study drug to treat a complication of the disease which leads to vision loss. The name of the study drug is rAAV.sFlt-1.

This experimental study uses a non-pathogenic virus to express a therapeutic protein within the eye. The therapeutic diminishes the growth of abnormal blood vessels under the retina. The duration of effect is thought to be long-term (years) following a single administration.

The clinical research study will look at the baseline safety and efficacy of a single injection of rAAV.sFlt-1 injected directly into the eye.

Approximately forty (40) subjects will participate in Australia. The primary endpoint of the study is at one month, with extended follow up for 3 years.

Phase Phase 1
Phase Phase 2
Study type Interventional
Study design Treatment
Study design Randomized
Study design Single Blind (Outcomes Assessor)

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Study design	Parallel Assignment
Study design	Safety/Efficacy Study
Primary outcome	Measure: No sign of unresolved ophthalmic complications, toxicity or systemic complications as measured by laboratory tests from 1 month post injection Time Frame: Primary endpoint at 1 month Safety Issue? Yes Description: 1) Ocular examination: - Ocular inflammation - Intraocular pressure - Visual acuity - Retinal bleeding 2) Abnormal laboratory data
Secondary outcome	Measure: Maintenance or improvement of vision without the necessity of ranibizumab re-injections Time Frame: Up to 3 years Safety Issue? No Description: 1) Best-corrected visual acuity 2) CNV lesion 3) Foveal thickness
Enrollment	40 (Anticipated)
Condition	Macular Degeneration
Condition	Age-related Maculopathies
Condition	Age-related Maculopathy
Condition	Maculopathies,Age-related
Condition	Maculopathy,Age-related
Condition	Retinal Degeneration
Condition	Retinal Neovascularization
Condition	Eye Diseases
Arm/Group	Arm Label: Low Dose rAAV.sFlt-1 Experimental
Arm/Group	Arm Label: High Dose rAAV.sFlt-1 Experimental
Arm/Group	Arm Label: Control - ranibizumab only Active Comparator
Intervention	Biological/Vaccine: rAAV.sFlt-1 Arm Label: Low Dose rAAV.sFlt-1 1 x 10^10 vector genomes (vg) rAAV.sFlt-1, delivered by subretinal injection
Intervention	Biological/Vaccine: rAAV.sFlt-1 Arm Label: High Dose rAAV.sFlt-1

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1 x 10^11 vector genomes (vg) rAAV.sFlt-1, delivered by subretinal injection

Intervention Other: Control (ranibizumab alone) Arm Label: Control - ranibizumab only

Patients will not receive rAAV.sFlt-1, but will be eligible for retreatment with ranibizumab (Lucentis).

Recruitment Information

Status Active, not recruiting

Start date 2011-12

Last follow-up date 2017-05 (Anticipated)

Primary completion date 2015-05 (Anticipated)

Criteria

Inclusion Criteria:
• Age greater than or equal to 55 years;
• Subfoveal CNV secondary to AMD and with best corrected visual acuity of 3/60 - 6/9 with 6/60 or better in the other eye;
• Fluorescein angiogram of the study eye must show evidence of a leaking subfoveal choroidal neovascular lesion, or CNV currently under active management with anti-VEGF therapy;
• Must be a candidate for anti-VEGF intravitreal injections;
• No previous retinal treatment of photodynamic therapy or laser;
• Able to provide informed consent;
• Able to comply with protocol requirements, including follow-up visits.

Exclusion Criteria:
• Liver enzymes > 2 X upper limit of normal;
• Any prior treatment for AMD in the study / control eye, excluding anti-VEGF injections;
• Extensive sub-foveal scarring, extensive geographic atrophy, or thick subretinal blood in the study eye as determined by the investigator;
• Significant retinal disease other than sub-foveal CNV AMD;

Gender Both

Minimum age 55 Years

Healthy volunteers No

Administrative Data

Organization name Lions Eye Institute, Perth, Western Australia

Organization study ID 2008-135

Sponsor Lions Eye Institute, Perth, Western Australia

Collaborator Avalanche Biotechnologies, Inc.

Health Authority Australia: Department of Health and Ageing Therapeutic

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Goods Administration